Tuberculosis and Co-Morbidities

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Has the following disclosures to make:

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- No relevant financial relationships with any commercial companies pertaining to this activity

Tuberculosis and Co-Morbidities

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No Relevant Disclosures

Objectives

- Review three specific comorbid conditions' impact on diagnosis, management and treatment of people with TB
  - Diabetes
  - Liver Disease
  - TNF-alpha inhibitors

TB and Diabetes

The Diabetes Atlas

589 million adults (20-79 years) are living with diabetes worldwide

2024

Explore diabetes around the world

Data by region | Data by country

United States

2000	15.3 million
2011	23.7 million
2024	38.5 million
2050	43.0 million

NHANES 2017-2020

https://diabetesatlas.org

Global Impact of Co-Morbid Conditions on TB cases

Table 1. Global estimates of TB episodes in 2022 attributable to health-related risk factors published in the Global TB Report.

Risk factor	Risk ratio (uncertainty interval)		Number of people with the risk factor (millions)	Attributable TB episodes (millions, uncertainty interval)	
Alcohol use disorders	3.3	(2.1 to 5.2)	297	0.73	(0.52 to 0.99)
Diabetes	1.5	(1.3 to 1.8)	509	0.37	(0.27 to 0.48)
HIV infection	14	(12 to 16)	39	0.89	(0.73 to 1.1)
Smoking	1.6	(1.2 to 2.1)	998	0.70	(0.50 to 0.95)
Undernourishment	3.2	(3.1 to 3.3)	711	2.2	(2.0 to 2.4)

Cold Spring Harb Perspect Med. 2026 Jun 29:a041894. doi: 0.1101/cshperspect.a041894.

Association between diabetes mellitus and tuberculosis:

A systematic review and meta-analysis

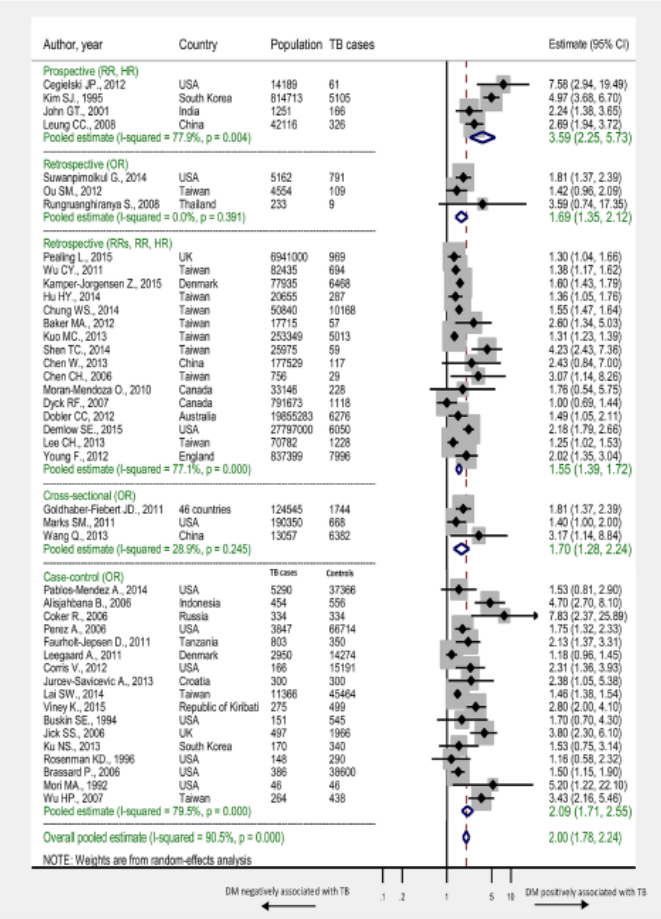


Fig 2. Forest plot of the meta-analyses. Pooled findings of 44 studies reporting adjusted estimates of the association between TB and DM, stratified according to study design. Size of the square is proportional to the precision (weight) of the study-specific effect estimates. Circle is the study–specific effect point estimate. Arrows indicate that the bars are truncated to fit the plot. The diamond is centered on the summary effect estimate, and the width indicates the corresponding 95% CI. RRs: relative risk; RR: rate ratio; OR: odds ratio; HR: hazard ratio.

Increase in risk

- By study type
  - 3.59-fold (prospective)
  - 1.55-fold (retrospective)
  - 2.09-fold (case-control)
- By country income level
  - 3.16 fold low/middle income vs. 1.73-fold in high income
- By geographical region
  - 2.44-fold in Asia
  - 1.71-fold in Europe
  - 1.73-fold in USA/Canada

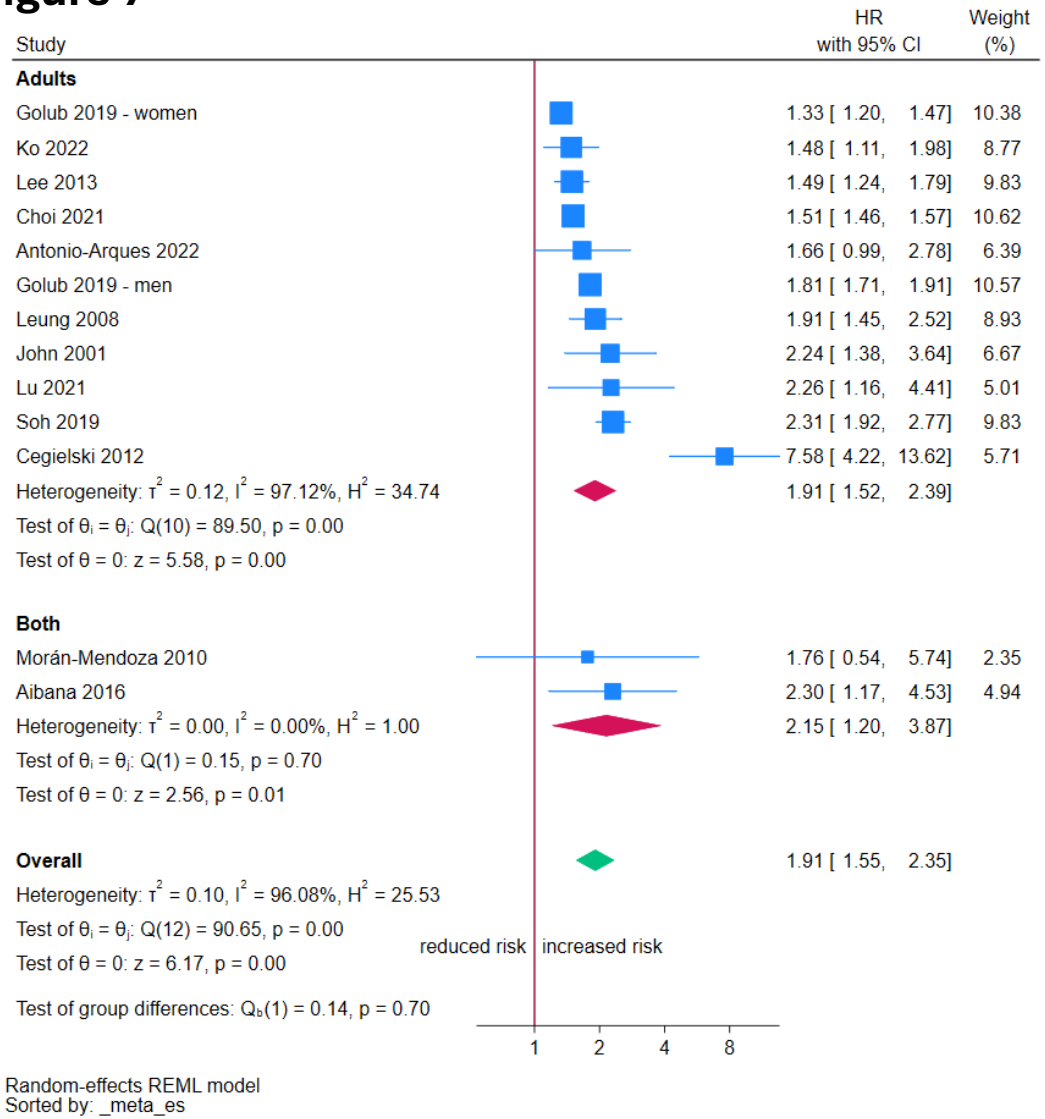
Conclusion:

DM is associated with a 1.5-fold- to 4-fold increased risk TB

Al-Rifai et al. PLoS ONE 12(11): e0187967

Diabetes as a Risk Factor for Tuberculosis Disease

Figure 7



DM is associated with a 1.9 fold increased risk TB

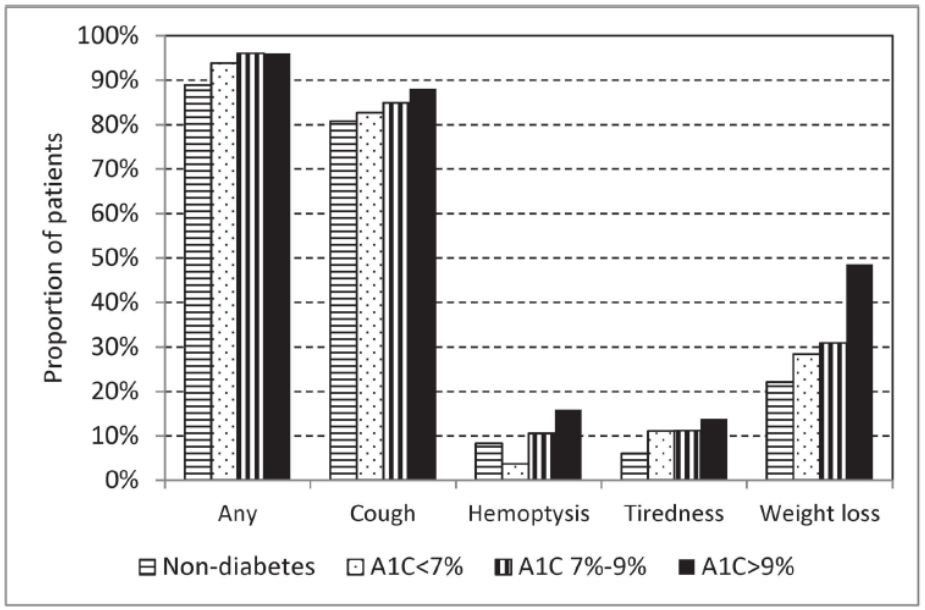
Cold Spring Harb Perspect Med. 2026 Jun 29:a041894. doi: 0.1101.

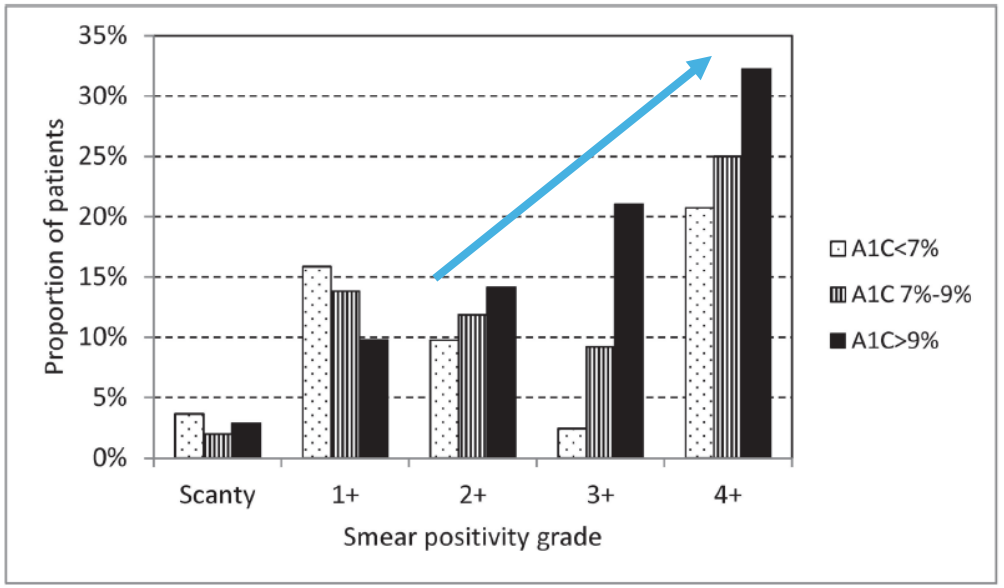
PLOS ONE

RESEARCH ARTICLE

The Influence of Diabetes, Glycemic Control, and Diabetes-Related Comorbidities on Pulmonary Tuberculosis

Chen Yuan Chiang[1,2,3], Kuan Jen Bai[2,4], Hsien Ho Lin[5], Shun Tien Chien[6], Jen Jyh Lee[7], Donald A. Enarson[1], Ting-I Lee[8,9], Ming-Chih Yu[2,4]*





Chiang et al. PLoS ONE 2015 10(3): e0121698

TB and Diabetes – Glycemic Control Matters

Effect of glycemic control on tuberculosis treatment outcomes among patients with tuberculosis and diabetes mellitus: A systematic review and meta-analysis

Maham Zahid, Saima Afaq, Kashif Shafique, Fatima Khalid Qazi, Urooj Ashfaq, Muhammad Asim, Shaista Nooreen, Sofia Shehzad

First published: 23 June 2025 | https://doi.org/10.1111/tmi.14140 | VIEW METRICS

Study or Subgroup	Uncontrolled HbA1c (≥ 7%) Events	Total	Controlled HbA1c (<7%) Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Mahishale V et al., (2017)	153	423	9	207	22.4%	8.32 [4.34, 15.96]
Mi F et al., (2013)	14	55	4	31	19.7%	1.97 [0.71, 5.47]
Nandakumar KV et al., (2013)	38	103	22	68	23.7%	1.14 [0.74, 1.75]
Park SW et al., (2012)	6	28	3	24	17.6%	1.71 [0.48, 6.13]
Yoon YS et al., (2017)	17	47	17	47	16.6%	8.50 [2.08, 34.76]
Total (95% CI)		656		377	100.0%	2.97 [1.10, 8.07]
Total events	228		40			

Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 28.86$, df = 4 ($P < 0.00001$); $I^2 = 86\%$

Test for overall effect: Z = 2.14 (P = 0.03)

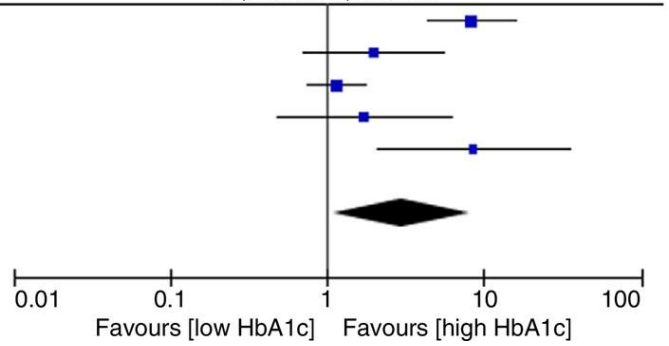


Figure 4. Forest plot comparing risk of sputum smear positivity at 3 months among patients with controlled and uncontrolled diabetes mellitus. CI, confidence intervals.

Diabetes Impacts TB Treatment and Cure

Meta-Analysis > Int J Tuberc Lung Dis. 2019 Jul 1;23(7):783-796. doi: 10.5588/ijtld.18.0433.

The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis

There is an association between diabetes and

- MDR-TB OR 1.98*
- Treatment failure OR 1.7*
- Relapse and recurrence OR 1.64, 95% CI 1.29–2.08
- Mortality OR 1.88, 95% CI 1.59 – 2.21

* Significant heterogeneity across studies

TB and Diabetes – Pharmacokinetic Considerations

Meta-Analysis > Int J Tuberc Lung Dis. 2024 Sep 1;28(9):454-460. doi: 10.5588/ijtld.23.0507.

A systematic review on the effect of diabetes mellitus on the pharmacokinetics of TB drugs

Rifampin Tmax was significantly prolonged in those with diabetes compared to those without diabetes

* No difference in the Cmax
* No difference in the AUC

TB and Diabetes – Management Considerations

- **Rifampin interacts with** many of the older (affordable) hypoglycemic medications
  - Glipizide, glyburide, glimepiride, sitagliptin, pioglitazone (reduced efficacy)
  - Enzyme induction reaches steady state ~1–2 weeks after starting rifampicin and dissipates over ~2 weeks after stopping.
  - Core principal = proactive glucose monitoring with anticipatory dose adjustment both when rifampicin is started when it is stopped
  - Rifampin DOES NOT interact with Metformin
- **Diabetic neuropathy** at baseline complicates therapy due to INH-related neuropathy
  - Baseline assessment of neuropathy
  - Vitamin B 6 (pyridoxine) to all those with diabetes taking INH or ethionamide
- **Ethambutol ocular toxicity** may be more frequent or additive with diabetic complications
  - Baseline assessment of visual acuity
- **Renal insufficiency** is associated with diabetes, especially long standing or poorly controlled diabetes
  - Adjust dose and dosing interval of EMB and PZA in those with Creatinine Cl < 30

TB and Diabetes – Rifampin

Interaction Magnitude with Rifampin

Antidiabetic class	Effect of rifampicin	Clinical implication	References
Sulfonylureas (glyburide, glipizide, glimepiride, tolbutamide, chlorpropamide)	↑ hepatic (CYP2C9) metabolism; glyburide AUC ↓~39%, glipizide ↓~22%; glyburide hypoglycemic effect blunted	Monitor glucose; may need dose ↑ or switch to alternate agent; wide interindividual variability makes titration difficult	[1-2, 5]
Meglitinides (repaglinide, nateglinide)	Repaglinide AUC ↓31–57% (glycemic effect variable); nateglinide AUC ↓~24% (little glycemic effect)	Monitor; repaglinide effect may be reduced	[1, 5]
Thiazolidinediones (rosiglitazone, pioglitazone)	Rosiglitazone concentrations ↓54–65% (CYP2C8); pioglitazone ↓~54%	Reduced efficacy likely; monitor glucose	[1]
Metformin	Not CYP-metabolized; rifampicin ↑OCT1 expression/hepatic uptake → AUC ↑~28%, Cmax ↑~19%, but blood glucose unchanged	No dose change or extra glucose monitoring needed for the interaction itself; preferred agent	[4, 6-7]
DPP-4 inhibitors	Only slight effect	Minor; usually no adjustment	[7]
GLP-1 receptor agonists	Probably no effect	No adjustment expected	[7]
Insulin	Not metabolized → no PK interaction (though rifampicin's direct glycemic effects may ↑ requirements)	Preferred for severe hyperglycemia; no rifampicin PK interaction	[1, 7]

1. The Lancet. Infectious Diseases. 2009. Dooley KE, Chaisson RE; 2. Clinical Pharmacokinetics. 2003. Niemi M et al.; 4. The International Journal of Tuberculosis and Lung. 2018. van Crevel R et al; 5. Clinical Infectious. 2016. Nahid P et al. 6. Clinical Pharmacology and Therapeutics. 2019. Te Brake LHM et al; 7. The Lancet. Diabetes & Endocrinology. 2014. Riza AL et al.

Yu et al. BMC Infectious Diseases (2019) 19:859
https://doi.org/10.1186/s12879-019-4548-4

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

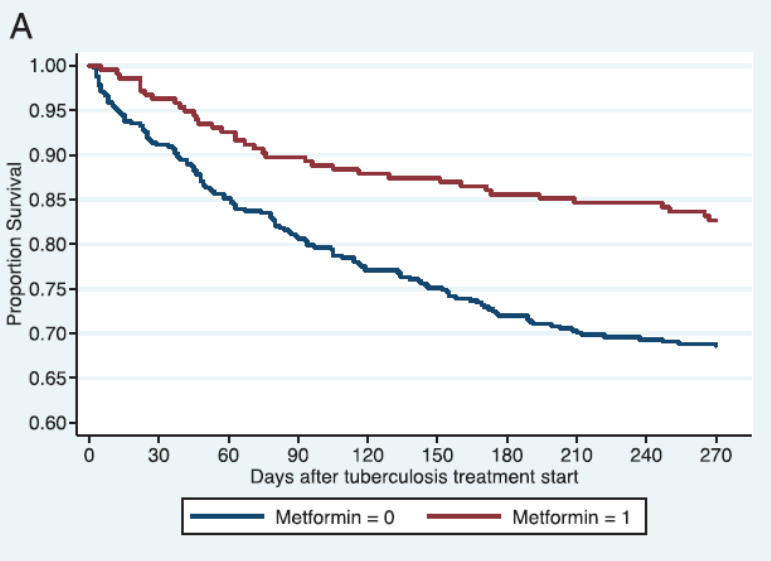
Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review

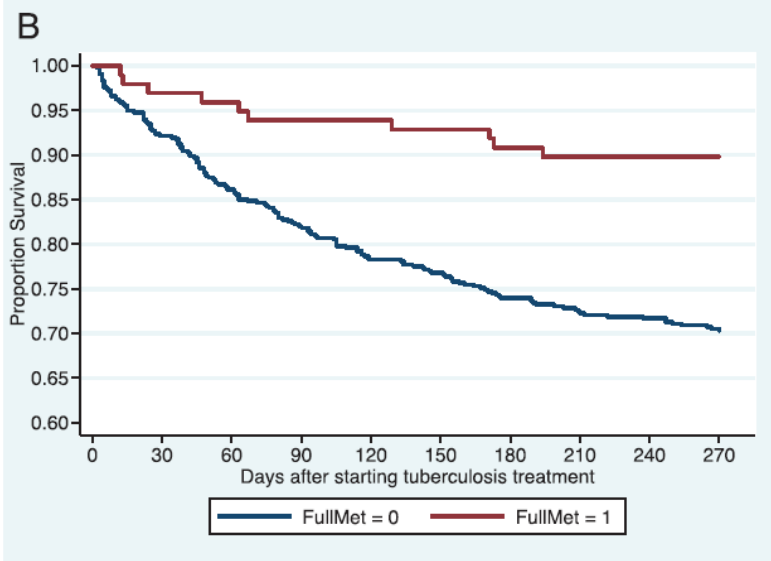
Xinyu Yu[1†], Ling Li[2†], Liangtao Xia[1], Xin Feng[1], Fan Chen[3], Shiyi Cao[3*] and Xiang Wei[1,4,5,6*]

- Retrospective review of databases through March 2019
- 12 observational studies, 6980 cases

- Results
  - Metformin prescription was not related to lower risk of TB infection
  - Metformin prescription decreased risk of TB among diabetics (TBI to TB disease)
  - Metformin use resulted in higher probability of smear conversion at 2 months
  - Metformin medication during treatment for TB disease reduced mortality
  - Relapse was not reduced by metformin prescription

Metformin use reverses the increased mortality associated with diabetes mellitus during tuberculosis treatment





	Metformin (n=216)	Non-Metformin (n=418)	Total (n=634)	Log-Rank χ2
Death during tuberculosis treatment -%	17.6	31.3	26.7	<0.001

	Metformin (n=219)	Non-Metformin (n=358)	Total (n=577)	Log-Rank χ2
Death during tuberculosis treatment -%	10.2	29.7	26.7	<0.001

Degner et al. CID 2018; 66(2):198–205

Metformin associated with lower TB mortality in those with TB and DM patients

Meta-Analysis > Eur J Clin Pharmacol. 2020 Feb;76(2):149-159.
doi: 10.1007/s00228-019-02786-y. Epub 2019 Nov 30.

Impacts of metformin on tuberculosis incidence and clinical outcomes in patients with diabetes: a systematic review and meta-analysis

Two studies, 889 people those taking metformin vs those taking no metformin

RR 0.34, 95% CI 0.20–0.57

Metformin associated with fewer residual cavitary lesions on CXR and lower inflammatory markers

Randomized Controlled Trial > Clin Infect Dis. 2022 Aug 31;75(3):425-434.
doi: 10.1093/cid/ciab964.

Randomized Trial of Metformin With Anti–Tuberculosis Drugs for Early Sputum Conversion in Adults With Pulmonary Tuberculosis

Primary endpoint = time to sputum culture conversion –

Median time to culture conversion unchanged
(42 vs 41 days; HR 0.8, 95% CI 0.62–1.02)

Plasma inflammatory markers and time to CXR clearance also measured –

Fewer residual cavitary lesions on X-ray
(5.3% vs 12.9%; RR 0.42, P=0.041)
Lower inflammatory markers
(TNFalpha, IL17-a, CRP. A-2 macroglobulin)

TB and the Liver

Cirrhosis and Tuberculosis

Cirrhosis changes TB susceptibility, presentation, diagnostic performance, and treatment risk.

Immune dysfunction

↑ primary infection
↑ LTBI reactivation

→

Atypical presentation

Classic chest imaging may be absent

→

Diagnostic uncertainty

TST/IGRA less reliable
→ delayed diagnosis

→

Treatment vulnerability

Hepatotoxicity can precipitate decompensation

Clinical implication

Treatment should be individualized using Child-Turcotte-Pugh or MELD severity while balancing TB control against hepatic decompensation.

Home › Digestive Diseases and Sciences › Article

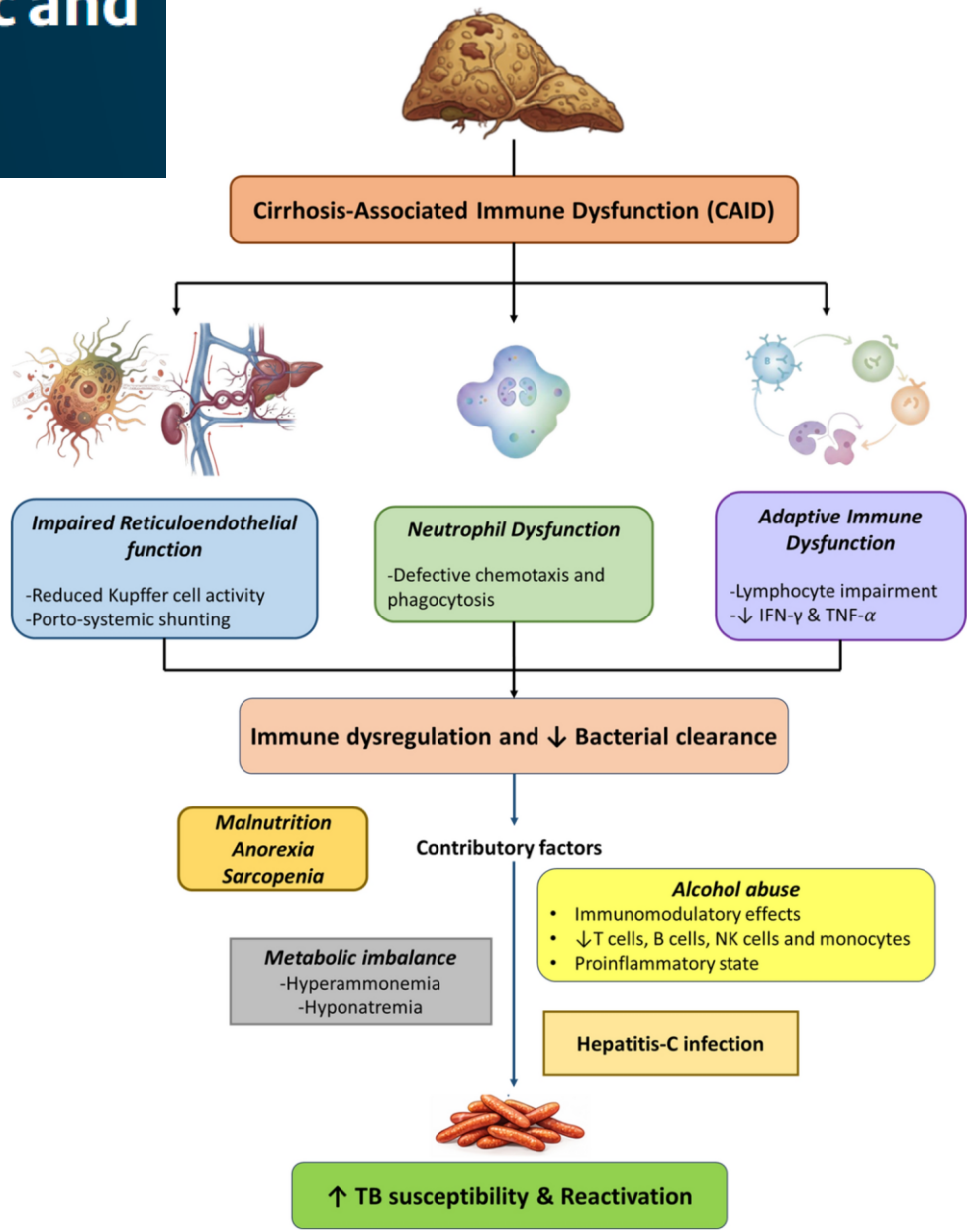
Tuberculosis in Cirrhosis: A Diagnostic and Therapeutic Challenge

Review | Published: 20 June 2026

Fig. 1.

Immune dysfunction

↑ primary infection
↑ LTBI reactivation



Preexisting Liver Disease Increases TB Treatment Risk

Reduced hepatic reserve increases the consequences of drug-induced liver injury (DILI) and complicates monitoring.

Who is at higher risk?

Advanced liver disease

Liver transplant

Hepatitis C infection

Baseline labs matter

Abnormal baseline aminotransferases are an independent risk factor for DILI.

Why it matters

With marginal hepatic reserve, superimposed DILI may be severe or life-threatening.

Baseline viral hepatitis screening

Screen for hepatitis B and C when risk factors are present, including injection drug use, birth in a hepatitis-endemic region, or HIV.

Source: [1]

Why First-Line TB Drugs Can Injure the Cirrhotic Liver

INH, RIF, and PZA biotransformation generates reactive intermediates that amplify existing hepatic vulnerability.

INH
Isoniazid

RIF
Rifampin

PZA
Pyrazinamide

→ **Reactive metabolites / intermediates**

Oxidative injury

Membrane peroxidation
+ oxidative stress

Mitochondrial injury

Mitochondrial dysfunction
+ apoptosis

Cholestasis

↓ bile salt export pump
↓ MRP2

Steatosis

Lipid accumulation
within hepatocytes

Net effect: multiple overlapping injury pathways compound hepatotoxicity in a liver with reduced functional reserve.

How Liver Disease Changes Regimen Selection

Advanced disease or baseline ALT >3× ULN (when not attributable to TB) favors regimens with fewer hepatotoxic drugs.

Preserve the core drugs when possible

INH and especially RIF are crucial to treatment efficacy. Preexisting liver disease alone does not automatically require their removal.

Reduce hepatotoxic burden when necessary

Select fewer hepatotoxic agents in advanced liver disease or when baseline ALT is >3× ULN for a non-TB reason.

Treatment principle

1. **Retain RIF** highest priority
2. **Retain INH** if hepatic reserve permits
3. **Consider removing PZA** frequently implicated in DILI
4. **Use expert consultation** for advanced disease / modified regimens

Monitoring TB Therapy in Preexisting Liver Disease

Underlying liver disease and hepatic TB can obscure whether abnormal liver tests represent DILI.

Why monitoring is difficult

Aminotransferases and bilirubin may fluctuate from the underlying liver disease itself.

TB can mimic DILI

Hepatic TB can elevate aminotransferases; these abnormalities may improve with effective TB treatment.

Lower hepatic reserve

A new drug-related injury may be clinically more consequential in patients with advanced impairment.

Recommended laboratory surveillance

Measure serum aminotransferases and total bilirubin every 1–4 weeks for at least the first 2–3 months; add periodic INR when hepatic impairment is severe.

When Should Hepatotoxic TB Drugs Be Stopped?

Standard DILI thresholds apply, but cirrhosis may justify a more conservative approach.

ALT ≥3× ULN + hepatitis symptoms

Suspect DILI → stop all hepatotoxic TB drugs immediately.

ALT ≥5× ULN without symptoms

Suspect DILI → stop all hepatotoxic TB drugs immediately.

Cirrhosis or hepatic encephalopathy

ALT interruption thresholds are not well defined. Some experts interrupt therapy for even a 3-fold ALT elevation, regardless of symptoms.

Source: [1]

MASH/MASLD Increases Antituberculosis DILI Risk

The principal effect is increased hepatic toxicity and monitoring burden—not worse TB treatment success.

23.3%

AT-DILI
28 of 120 patients

Clinical pattern

Most commonly hepatocellular and generally mild; 1 acute liver failure.

Early onset

Mean onset ≈30 days after anti-TB treatment initiation.

Higher-than-usual burden

Clinically significant DILI is less common in unselected patients on standard 4-drug therapy.

Practical implication

MASH/MASLD warrants closer hepatic monitoring, especially early in therapy.

Retrospective study examined patients with pulmonary tuberculosis MASLD

› Medicine (Baltimore). 2025 Aug 29;104(35):e44078. doi: 10.1097/MD.0000000000044078.

Influence of metabolic dysfunction–associated steatotic liver disease on antituberculosis drug–induced liver injury

Open Forum Infect Dis. 2023 Aug 7;10(8):ofad422. doi: 10.1093/ofid/ofad422. eCollection 2023 Aug.

Metabolic Disorders Are Associated With Drug-Induced Liver Injury During Antituberculosis Treatment: A Multicenter Prospective Observational Cohort Study in Korea

Prospective multicenter cohort: 684 patients with drug-susceptible TB

7.6%
developed DILI

92.9%
of DILI cases had metabolic disorders

aHR 2.85
metabolic disorders
95% CI 1.01–8.07

Who is at risk?

Metabolic disorders included insulin resistance, hypertension, obesity, or dyslipidemia.

Risk was greatest for significant ALT elevation during the first month.

TB efficacy remains preserved

Treatment outcome was not affected by metabolic disorder status.

Clinical focus: anticipate and manage hepatotoxicity while maintaining curative TB therapy.

Bottom line: metabolic dysfunction affects hepatic tolerability more than TB microbiologic outcome.

January 2023

Clinical Infectious Diseases

MAJOR ARTICLE

Association of Treated and Untreated Chronic Hepatitis C With the Incidence of Active Tuberculosis Disease: A Population-Based Cohort Study

Davit Baliashvili,[1] Henry M. Blumberg,[1,2] David Benkeser,[3] Russell R. Kempker,[2] Shaun Shadaker,[4] Francisco Averhoff,[5] Lia Gvinjilia,[6] Natalia Adamashvili,[7] Matthew Magee,[8] George Kamkamidze,[9] Mamuka Zakalashvili,[10] Tengiz Tsertsvadze,[11] Lali Sharvadze,[12,13] Mamuka Chincharauli,[14] Nestan Tukvadze,[14] and Neel R. Gandhi[1,2,8]

Study aim: Assess how untreated and treated chronic HCV infection status impacts the incidence of active TB disease.

Hypothesis: Incidence of active TB is highest among those with untreated chronic HCV infection followed by those who were treated and lowest among those never infected with HCV

- Conducted cohort study among adults in Georgia tested for HCV from 1/1/2015 – 9/30/2020. Excluded those with known diagnosis of active TB disease before or at time of first HCV test.
- **Results:** Incidence rate/1000,000 person-years:
  - Untreated HCV – 296 **> 4 times higher than never infected**
  - Treated HCV - 109 1.7 times higher than never infected
  - HCV negative - 65

Alcohol Misuse and TB

Review > BMC Public Health. 2009 Dec 5:9:450. doi: 10.1186/1471-2458-9-450.

The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review

> Addiction. 2017 Dec;112(12):2124-2131. doi: 10.1111/add.13926. Epub 2017 Aug 22.

Heavy alcohol consumption increases the risk of active tuberculosis in Taiwanese adults: a nation-wide population-based cohort study

Meta-Analysis > Int J Tuberc Lung Dis. 2018 Nov 1;22(11):1277-1285. doi: 10.5588/ijtld.18.0092.

Alcohol consumption and risk of tuberculosis: a systematic review and meta-analysis

Observational Study > PLoS One. 2020 Dec 17;15(12):e0240595.
doi: 10.1371/journal.pone.0240595. eCollection 2020.

Alcohol use and tuberculosis clinical presentation at the time of diagnosis in Puducherry and Tamil Nadu, India

Individuals with heavy alcohol consumption or alcohol use disorder (AUD) have a two- to five-fold increased risk of developing active TB compared to those who do not drink alcohol.

Alcohol Misuse and TB

Differences in disease characteristics between North Carolina tuberculosis cases reported 1994–2006 with and without excess alcohol use

Characteristic	Excess alcohol use		Prevalence ratio (95% confidence interval)
	Yes	No/unknown	
Site of disease			
Pulmonary (±extrapulmonary)	1227 (92.5%)	3266 (77.2%)	1.20 (1.17–1.23)
Extrapulmonary only	99 (7.5%)	964 (22.8%)	
Chest radiographic findings			
Cavitary	452 (36.8%)	920 (28.2%)	1.31 (1.19–1.43)
Non-cavitary	775 (63.2%)	2346 (71.8%)	
Sputum smear			
Positive	809 (65.9%)	1495 (45.8%)	1.44 (1.36–1.52)
Negative	418 (34.1%)	1771 (54.2%)	
Sputum culture			
Positive	1038 (84.6%)	2270 (69.5%)	1.22 (1.18–1.26)
Negative	189 (15.4%)	996 (30.5%)	

Chest radiographic, sputum smear, and sputum culture data are for cases with pulmonary involvement only.

› Int J Tuberc Lung Dis. 2012 Jul;16(7):886-90. doi: 10.5588/ijtld.11.0624. Epub 2012 May 8.

Tuberculosis and alcohol misuse in Scotland: a population-based study using enhanced surveillance data

B de la Haye [1], S H Wild, J Stevenson, F Johnston, O Blatchford, I F Laurenson

Pulmonary Disease: 92.3% vs 61.1%

Fiske et al Journal of Infection (2009) 58, 395-401

Alcohol Misuse and TB

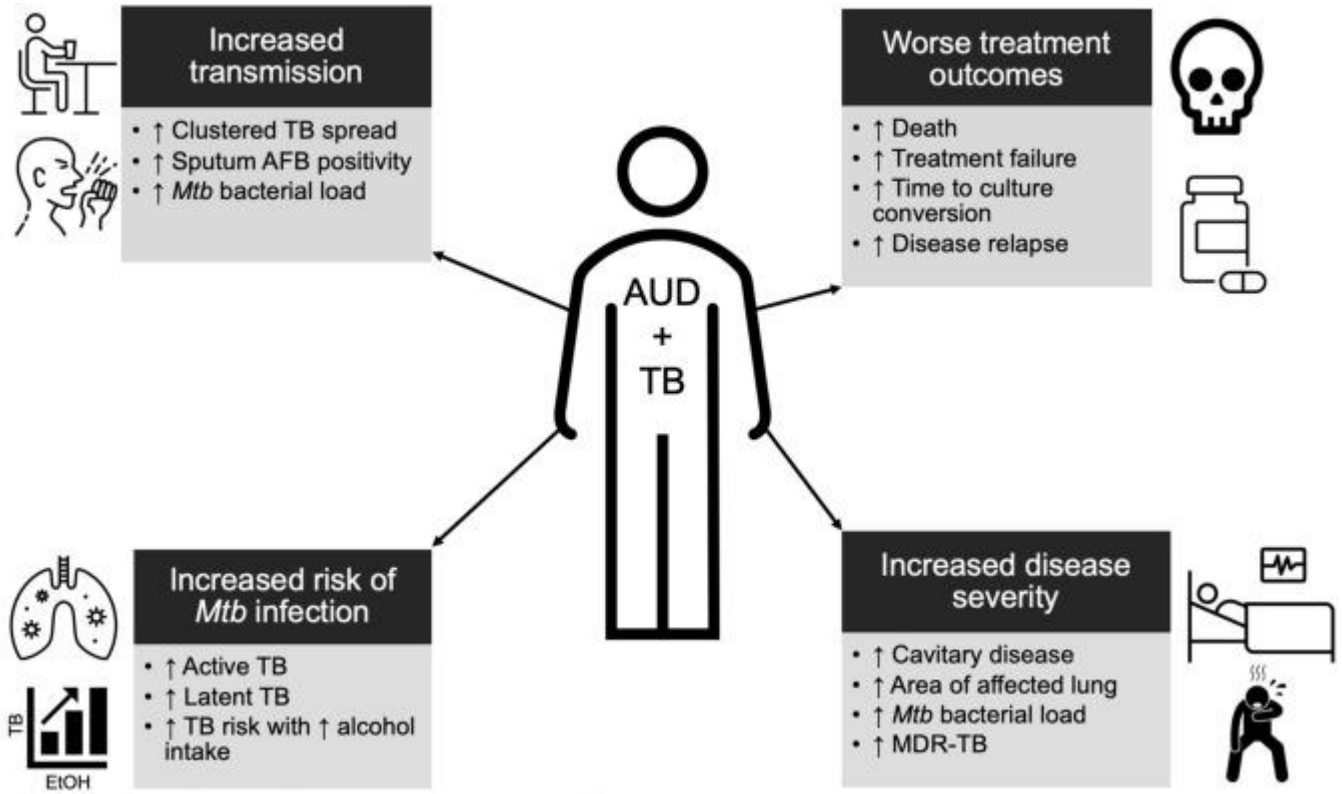


Figure 1

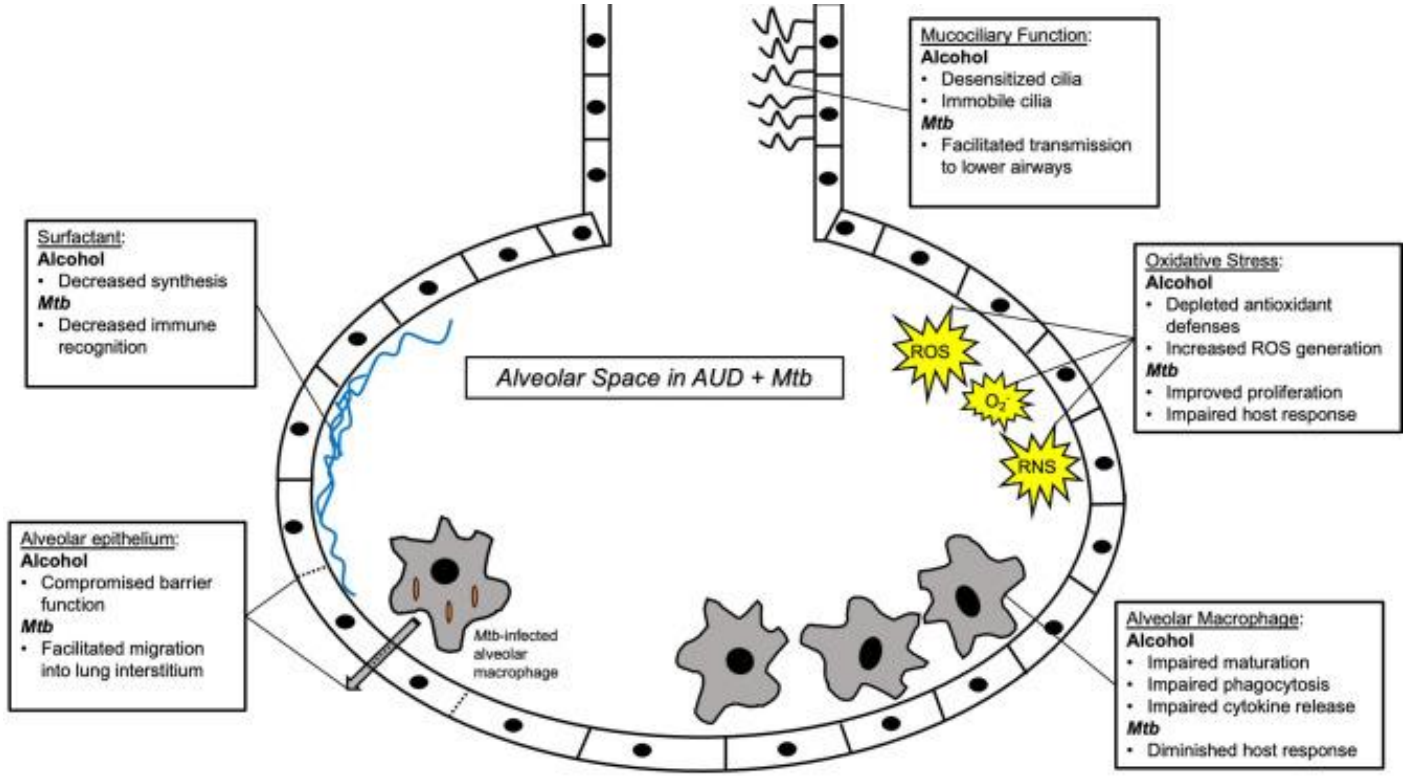
Summary schema of the epidemiologic data of alcohol use disorder (AUD) and tuberculosis (TB). Individuals with AUD are at a higher risk for TB, more infectious, have more severe disease, and are more likely to experience poor outcomes.

Gregory Wigger et al. Front Immunol. 2022 Mar 31:13:864817

Review > Front Immunol. 2022 Mar 31:13:864817. doi: 10.3389/fimmu.2022.864817.
eCollection 2022.

The Impact of Alcohol Use Disorder on Tuberculosis: A Review of the Epidemiology and Potential Immunologic Mechanisms

Gregory W Wigger [1], Tara C Bouton [2], Karen R Jacobson [2], Sara C Auld [1 3], Samantha M Yeligar [1 4], Bashar S Staitieh [1]



Alcohol and Hepatotoxicity in the Treatment of TB Disease

Table 5 Dichotomous variables in cases and controls

	Cases (n = 86)	*Controls (n = 406)*	*χ^2†*	*Odds ratio (95% CI)*
High alcohol intake	19·8%	4·9%	20·4	4·76 (2·25 to 10·05)*
Extensive disease	14·0%	3·5%	13·6	4·5 (1·88 to 10·93)*
Slow acetylator	82·9%	64·2%	5·60	2·72 (1·16 to 6·57)**
Jaundice in past	11·6%	10·8%	0·001	1·08 (0·49 to 2·35)
Pyrazinamide in regimen	62·8%	25·1%	44·78	5·03 (2·99 to 8·47)***

* $p<0·001$; ** $p<0·01$; *** $p<0·1 \times 10^{-7}$.
† Yates' corrected χ^2.

Pande Thorax 1996;51:132-136

TB and TNF-alpha Inhibitors

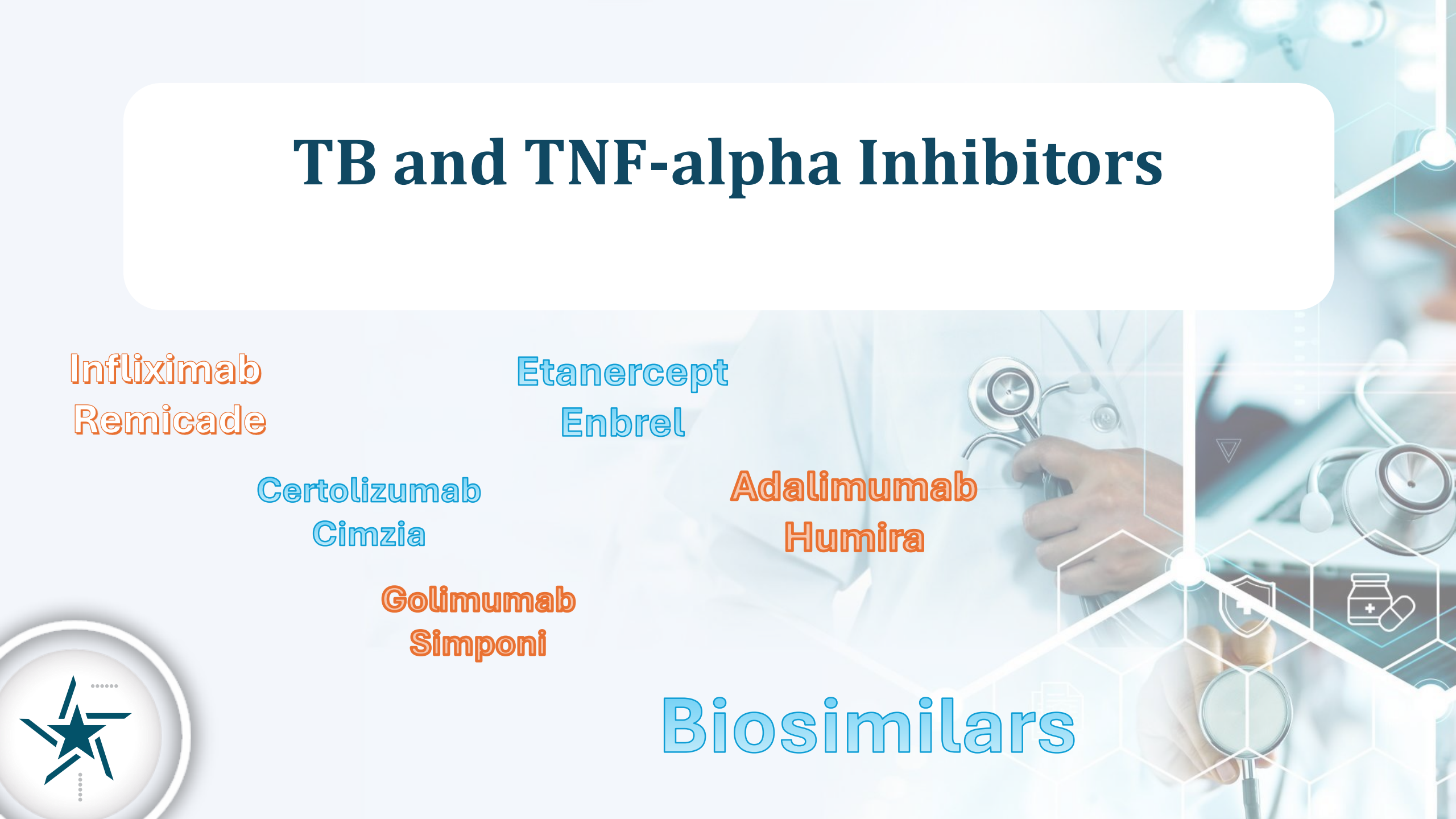
Infliximab
Remicade

Etanercept
Enbrel

Certolizumab
Cimzia

Adalimumab
Humira

Golimumab
Simponi



Biosimilars

TNF-α Inhibitors: Magnitude and Timing of TB Risk

TNF inhibition is the biologic class most strongly associated with tuberculosis.

2–4× higher risk

Most series show a two- to four-fold increase in active TB risk.

Up to ~25×

Relative risk can be substantially higher depending on the TNF inhibitor and background TB burden.

Predominantly reactivation

Most excess TB reflects reactivation of LTBI; new infection also contributes in endemic regions.

TB tends to occur early

A large proportion occurs within the first year.

Median time to event: ~5.5 months with infliximab and ~18.5 months with adalimumab.

Risk persists after stopping therapy

TB may present months after TNF inhibitor discontinuation.

Clinical vigilance should therefore extend beyond the treatment period.

Risk is shaped by agent, latent infection status, exposure, and local TB epidemiology.

ORIGINAL ARTICLE

Tuberculosis Associated with Infliximab, a Tumor Necrosis Factor α–Neutralizing Agent

Authors: Joseph Keane, M.D., Sharon Gershon, Pharm.D., Robert P. Wise, M.D., M.P.H., Elizabeth Mirabile-Levens, M.D., John Kasznica, M.D., William D. Schwieterman, M.D., Jeffrey N. Siegel, M.D., and M. Miles Braun, M.D., M.P.H. Author Info & Affiliations

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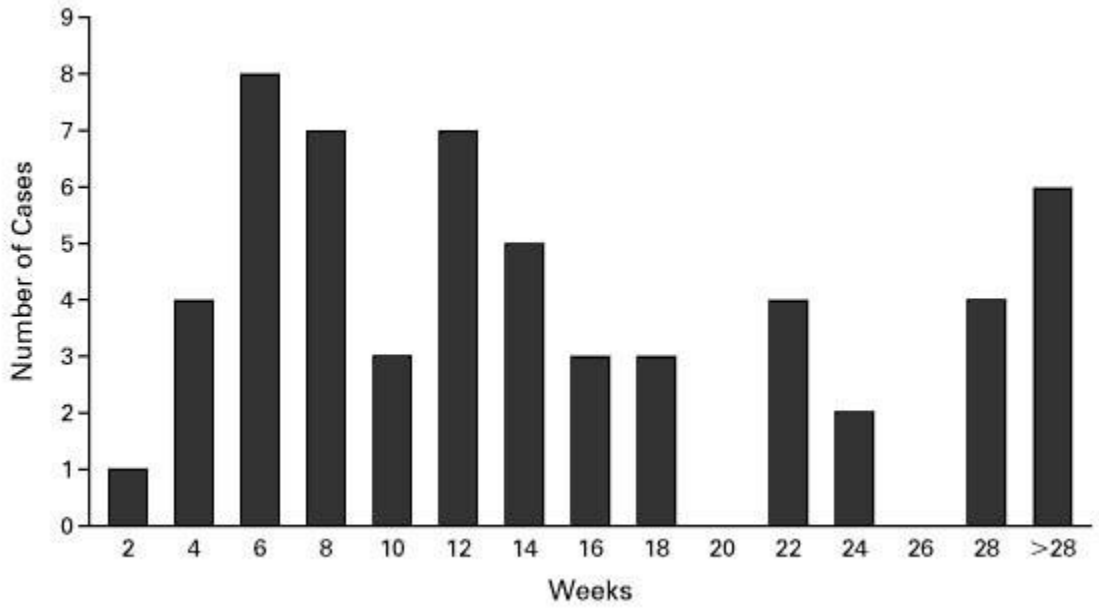
FIGURE 1

Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis.

Total = 57



H & E Stain

Apoptosis Stain

No TNFα

With TNFα

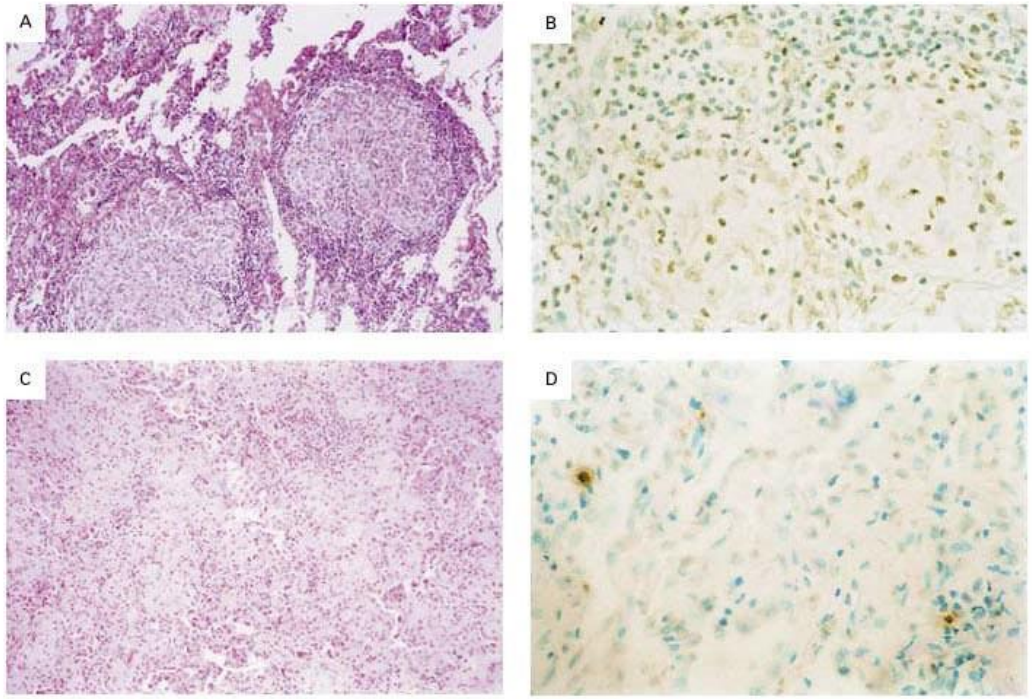
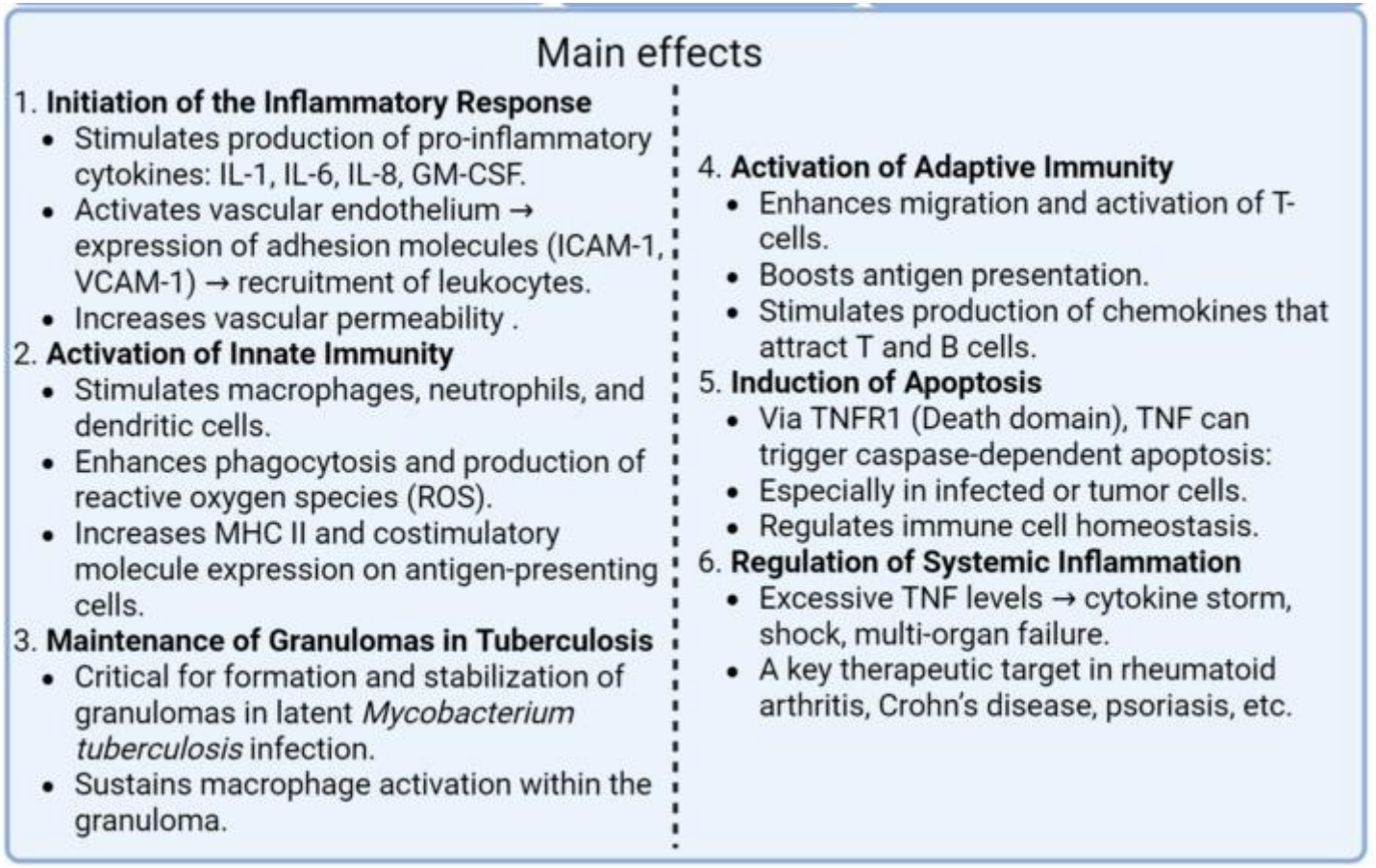


FIGURE 2

Photomicrographs of Lung Specimens from a Patient with Tuberculosis Who Did Not Receive Infliximab

Major Immunologic Effects of TNF During M. TB Infection



Biomolecules. 2025 May 12;15(5):709.
Doi: 10.3390/biom15050709

TB Risk Differs Among TNF-α Inhibitors

Comparative Study > Front Immunol. 2026 Jan 29:17:1726299.
doi: 10.3389/fimmu.2026.1726299. eCollection 2026.

Comparative risk of tuberculosis infection with different TNF-α inhibitors in immune-mediated inflammatory diseases: a systematic review and network meta-analysis

Infliximab	Highest
Adalimumab	High
Golimumab	Elevated
Etanercept	Lower
Certolizumab	Lowest

2025 network meta-analysis

19 cohorts • 396,044 patients

Risk ranking: infliximab > adalimumab > etanercept > certolizumab pegol

Certolizumab showed the lowest TB risk signal among TNF inhibitors.

Why might risk differ?

Infliximab/adalimumab: bivalent monoclonal antibody binding, complement fixation, and stronger effects on membrane-bound TNF.

Etanercept: soluble receptor with a lower observed TB signal.

Certolizumab: absence of an Fc portion may contribute to lower risk.

Review > Biomolecules. 2025 May 12;15(5):709. doi: 10.3390/biom15050709.

Role of Tumor Necrosis Factor in Tuberculosis

TB During TNF Inhibition Often Has Atypical or Severe Features

Extrapulmonary, disseminated, and miliary disease are disproportionately represented.

~74%

miliary TB in one European pediatric cohort

Disease phenotype

Higher proportion of extrapulmonary, disseminated, and miliary TB.

Screening limitation

TST and IGRA may be falsely negative in immunosuppressed patients.

Exposure still matters

Active TB has occurred after negative baseline screening when a later contact was identified.

Clinical implication

Maintain suspicion for TB despite a prior negative screen, particularly after new exposure.

Screening and Prevention Substantially Reduce TB Risk

Baseline LTBI assessment and preventive therapy are the cornerstone of safe TNF inhibitor use.

~80% reduction

Structured LTBI screening programs reduce TB incidence by approximately 80%.

7-fold higher incidence

Failure to adhere to recommended screening is associated with markedly higher TB incidence.

After discontinuation

Continued TB monitoring is advised for up to ~6 months after stopping TNF inhibition.

Clin Infect Dis. 2025 Nov 19;82(5):e1023–e1035. doi: 10.1093/cid/ciaf628
Front Immunol. 2025 Feb 3:16:1494283. doi: 10.3389/fimmu.2025.1494283.

LTBI Treatment and Follow-up During TNF Inhibition

LTBI regimens

4 months rifampin (4R)

3 months isoniazid + rifampin (3HR)

3 months weekly isoniazid + rifapentine (3HP)

6–9 months isoniazid is an alternative when short-course therapy is unsuitable.

Starting/restarting TNF inhibition

TNF inhibitor therapy can generally begin after ~1–2 months of LTBI treatment; local protocols vary.

After prior/current TB, systematic review data suggest re-introduction is relatively safe.

Reported TB relapse: ~3.8% at median 8.5 months.

Routine re-screening: debated

A 20-year low-prevalence experience found no outcome benefit from dual testing or systematic repeat screening after a negative baseline test.

Use geography + exposure risk

Test conversion during therapy can reach ~9% and is higher in endemic settings—supporting risk-based rather than universal repeat testing.

Individualize regimen and re-screening based on drug interactions, comorbidities, geography, and new TB exposure.

References: [22–26]

Thank You